The Role of mRNA Translational Control in Tumor Immune Escape and Immunotherapy Resistance

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ABSTRACT

Tremendous advances have been made in cancer immunotherapy over the last decade. Among the different steps of gene expression, translation of mRNA is emerging as an essential player in both cancer and immunity. Changes in mRNA translation are both rapid and adaptive, and translational reprogramming is known to be necessary for sustaining cancer cell proliferation. However, the role of mRNA translation in shaping an immune microenvironment permissive to tumors has not been extensively studied. Recent studies on immunotherapy approaches have indicated critical roles of mRNA translation in regulating the expression of immune checkpoint proteins, tuning the secretion of inflammation-associated factors, modulating the differentiation of immune cells in the tumor microenvironment, and promoting cancer resistance to immunotherapies. Careful consideration of the role of mRNA translation in the tumor-immune ecosystem could suggest more effective therapeutic strategies and may eventually change the current paradigm of cancer immunotherapy. In this review, we discuss recent advances in understanding the relationship between mRNA translation and tumor-associated immunity, the potential mechanisms of immunotherapy resistance in cancers linked to translational reprogramming, and therapeutic perspectives and potential challenges of modulating translational regulation in cancer immunotherapy.

Introduction

Mammalian cells are estimated to use 20% to 35% of their energy in the process of protein synthesis (1). As the ultimate step in protein production, mRNA translation is a quintessential hub for the regulation of gene expression. Mounting evidence from studying neoplasia and immune cell functions suggests that mRNA translation, as a fast-responding process, may play an important role in the regulation of tumor progression, cell plasticity, chemotherapeutic resistance, and lineage commitment (2). The control of mRNA translation enables tumor cells to quickly adapt to acute microenvironmental changes by selectively translating differential subsets of mRNAs that may be beneficial for their survival or to abrogate anticancer immune responses (3). In addition, mRNA translation can directly or indirectly regulate the expression of immune checkpoint proteins (4–6), modulate tumor-associated peptide antigen production (7–9) and affect the functional differentiation of tumor-associated immune cell (10, 11) to evade immune surveillance or to resist immunotherapies. In this review, we first briefly revisit the mRNA translation machineries, we then highlight recent advances in the translational regulation of tumor-associated immune responses. Specifically, we discuss the impact of mRNA translation on both the intrinsic regulation of immune-checkpoint protein expression in tumor cells and microenvironmental immune-cell functions and how these mechanisms enable cancer cells to escape antitumor immune responses. We also discuss potential therapeutic strategies that target components of the mRNA translational machinery and future research directions in this emerging domain.

Cellular mRNA Translational Machinery

Eukaryotic mRNAs containing a cap structure, which is composed of the methylated guanosine (G) triphosphate (m7GpppX, X represents any base), at the 5′ terminus of their 5′ untranslated region (UTR; ref. 12). The typical length of 5′ UTRs is approximately 100 to approximately 220 nucleotides across species. Following the coding sequence of the mRNA, another stretch of untranslated nucleotides forms the 3′UTR, which is terminated by 20 to 200 adenines (the polyA tail). Both 5′UTR and 3′UTR participate in the regulation of mRNA translation.

The decoding of genetic messages from mRNAs to polypeptides occurs in three steps: initiation, elongation, and termination. The translation initiation step, intricately controlled by several initiation factors and various signaling pathways required for ribosome recruitment onto the considered mRNA, is the rate-limiting step of mRNA translation. Apart from approximately 10% of cellular mRNAs that are translated using alternative mechanisms (e.g., internal ribosomal entry site), the majority of mRNAs undergo cap-dependent translation initiation. Although the details of cap-dependent translation initiation remain controversial, a ribosomal scanning model is widely accepted. The secondary structure in the 5′UTR is a determinant of the translational initiation efficiency. A strong stem-loop structure in the 5′UTR can stall the scanning of the 40S ribosome subunit, therefore, increases the dwell time of ribosome on the corresponding mRNA (13). Alternative splicing within the 5′UTR is estimated to affect 13% of the mammalian transcriptome (14). The variations in the 5′UTR can affect

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the translational efficiency of different mRNA isoforms, thus impact the expression levels of corresponding isoforms. For instance, the transforming growth factor β 3 gene can produce 2 alternative transcripts, a 3.5 kilobase (kb) transcript with a very long 5′UTR and a 2.6 kb transcript with a much shorter 5′UTR. The presence of eleven upstream open reading frames (uORF) in the 5′UTR dramatically reduces the translation efficiency of the 3.5-kb transcript whereas the 2.6-kb isoform has a higher translational efficiency (15).

At the beginning of translational initiation, the eukaryotic initiation factor 4F (eIF4F) complex, comprising eIF4E, eIF4A, and eIF4G, binds directly to the cap structure at the terminus of the 5′UTR via the mRNA cap-binding protein eIF4E (16). In the steady state, eIF4E is mostly held in an inactive form by interacting with a eIF4E binding protein (4E-BP1 or 4E-BP2). Upon a stimulation signal, 4E-BPs are phosphorylated by mTORC1 and release eIF4E, enabling eIF4E to bind eIF4G (**Fig. 1**). Notably, eIF4E can be phosphorylated by upstream kinases, such as MAPK-interacting kinase 1 and 2 (MNK1/2). MNK1/2-dependent phosphorylation of eIF4E at serine 209 decreases the mRNA binding activity of eIF4E, therefore, promotes translation initiation by providing more free intracellular eIF4E proteins (17–20). By promoting mRNA translation, phosphorylation of eIF4E on serine 209 has been demonstrated to be necessary for eIF4E-driven transformation and tumor metastasis (21, 22). As a large scaffold protein, eIF4G interacts with the DEAD-box ATP-dependent RNA helicase eIF4A, which resolves the stem-loop structure in the 5′UTR and thus removes the impediment of such structure on the translation initiation. EIF4A thus facilitates the attachment of the 43S preinitiation complex at near the cap structure to initiate ribosome scanning and its access to the start codon AUG coding for the amino acid methionine. This is reflected by the fact that the more complex an mRNA's 5′ UTR secondary structure is, the more dependent that mRNA is on eIF4F complex for translation initiation. Accompanying the eIF4F complex formation, the formation of a 43S preinitiation ternary complex comprising 40S ribosomal subunits (**Fig. 1**), the methionyl transfer RNA (Met-tRNA) bounds to eIF2-GTP and eIF3 is tightly regulated by eIF2α (23). Upon the arrival of Met-tRNA at the AUG codon, the 60S ribosomal subunit forms a complex with the 40S subunit to yield the mature 80S ribosome, and thus initiate the mRNA translation elongation.

In addition to eIF4F-mediated translation initiation at the 5′UTR, the 3′UTR of the mRNA also actively participates in translation initiation. In particular, the poly(A) tail of the 3′UTR can be recognized by the polyA binding protein (PABP), which forms a complex with eIF4G and facilitates the circularization of mRNA [i.e., communication between the 5′ cap structure and the 3′ poly(A) tail; ref. 24]. This translation initiation factor-associated circularization could potentially increase the ability of translation initiation factors to stimulate subsequent steps in the mRNA translation initiation process. For example, eIF4E-eIF4G-PABP1 complex may have a stronger affinity to the 40S ribosome subunit than that of eIF4G alone and may further stimulate the eIF4A helicase activity. The circularization may also function as a proofreading mechanism that translation initiation factors only recognize intact and correctly processed mRNAs. In addition, the recycling of translation initiation factors may occur more efficiently under the condition of circularized mRNAs.

The regulation of mRNA translation offers cancer cells a fast and flexible way to control protein expression and thus adapt to stress conditions. As a nexus of oncogenic signaling cues (**Fig. 1**), aberrant mRNA translation is implicated in both tumorigenesis and tumor progression. Emerging evidence has shown that mRNA translation also participates in multiple levels of tumor immune responses, rendering mRNA translation as a potential therapeutic target for the improvement of antitumor immunity.

mRNA Translation Modulates Antitumor Immune Responses

Translational regulation of the immune checkpoint protein PD-L1 expression in cancer cells

The concept of an immune checkpoint is based on the inhibitory function of receptors expressed on immune effector cells and their corresponding ligands expressed by cancer cells or other stromal cells. Some of these receptor/ligand pairs include CTLA4/CD80-CD86, PD1/PD-L1, LAG3/MHC-II, and TIM3/CEACAM1 (25–27). The interactions between these receptors and their ligands activate inhibitory pathways in immune cells and lead to tumor tolerance. By targeting CTLA4/CD80-CD86 or PD1/PD-L1 interactions, antibody-based immunotherapies have revealed the expression of immune checkpoint proteins as a key mechanism for cancer cells to escape antitumor immunity. In particular, recent studies showed that cancer cells can adaptively upregulate the expression of PD-L1 upon chronic exposure to IFNγ to mitigate antitumor immunity (28). As a primary target of the anti-PD1 immunotherapy, the regulatory mechanisms of PD-L1 expression, such as transcriptional regulation, posttranslation modification, and protein degradation have been intensively explored (29). However, the regulation of PD-L1 expression at the translational level was underappreciated until several recent studies demonstrated that translational modulation at different levels is implicated in the regulation of PD-L1 expression.

The main factor controlling PD-L1 expression is the IFNγ-activated JAK/STAT1 pathway. Our recent work has shown that the eIF4F complex is required for the PD-L1 induction on tumor cells by controlling STAT1 mRNA translation (**Fig. 2**). Indeed, the 5′UTR of the STAT1 mRNA contains complex secondary structures that require the helicase eIF4A for the efficient initiation of mRNA translation (6). Several oncogenic pathways converge on the eIF4F complex and, as such, can lead to immune escape. Indeed, we showed that eIF4F activation in BRAF-mutant melanoma cells induced the expression of PD-L1 (6). In addition, both 4E-BP1 and eIF4E are regulated downstream of the PI3K/AKT pathway, implying that the loss of PTEN, which is a frequent oncogenic event that activates the PI3K/AKT pathway, also activates the eIF4F and thus potentially induces PD-L1 expression. This is in accordance with the fact that PTEN deficiency enhances the induction of PD-L1 expression upon IFNγ stimulation (30). It is now well established that the loss of PTEN is a major contributor to the anti-PD1 immunotherapy resistance in different types of cancers (31–33). Therefore, PTEN deficiency–induced immune evasion could be correlated with eIF4F activity in cancer cells. For example, Parsa and colleagues have previously demonstrated that PTEN loss can stimulate PD-L1 mRNA translation through 4E-BP1 phosphorylation in glioma cells (34). Further studies are required to reveal how PTEN loss, in association with eIF4F-mediated translation initiation, contributes to tumor immune escape.

Alternative translational regulation of PD-L1 expression has recently been reported to function in an integrated stress response (ISR)–dependent manner. ISR is a signaling pathway present in eukaryotic cells that reduces the cap-dependent mRNA translation via the phosphorylation of eIF2α, which allows the translation of mRNAs specifically implicated in the stress adaptation. Xu and colleagues recently identified specific inhibitory regulatory μORF elements in the 5′UTR of PD-L1 mRNA that compete with the primary ORF for translation, leading to reduced PD-L1 mRNA translation in the steady

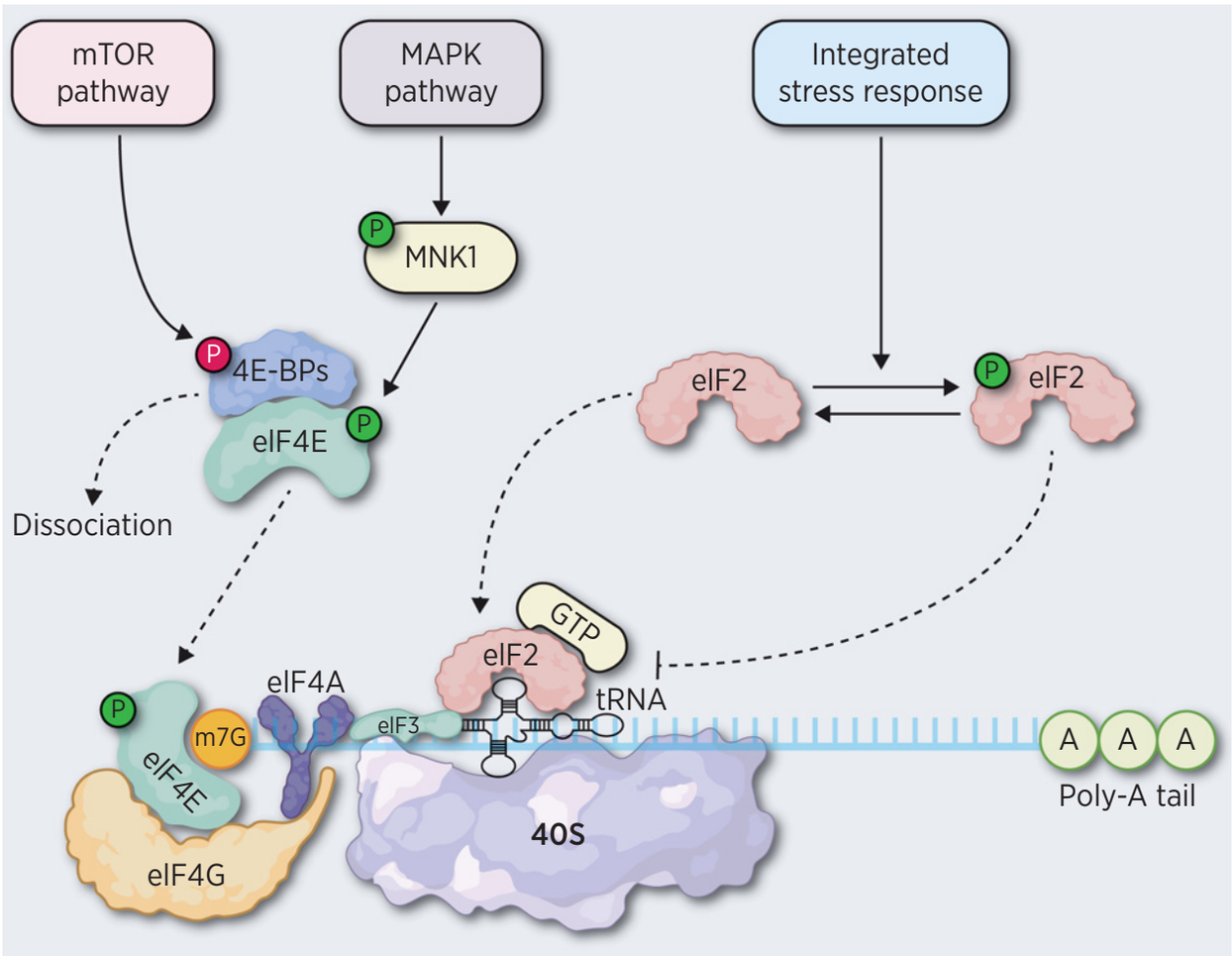

Figure 1.

Regulation of cap-dependent mRNA translation. The eIF4F complex is comprised of eIF4E, eIF4A, and eIF4G; it binds directly to the cap structure at the terminus of the 5′UTR of mRNA. eIF4E is maintained inactive by interacting with one of 4E-BPs, 4E-BP1 or 4E-BP2. After phosphorylation of 4E-BPs by mTORC1, eIF4E is released from 4E-BPs and is able to bind eIF4G. eIF4E can also be phosphorylated by upstream kinases such as MNK1/2, which further improve the cap-binding activity of eIF4E. Accompanying the eIF4F complex formation, 40S ribosomal subunits form a 43S preinitiation ternary complex with Met-tRNA bound with eIF2-GTP and eIF3, which is tightly regulated by eIF2α. Upon stress signals, cap-dependent mRNA translation is reduced via the phosphorylation of eIF2α. m7G, 7-methylguanosine; P, phosphorylation.

state. However, in a MYC/KRAS^{G12D} mutated liver tumor model, this inhibitory mechanism is bypassed via eIF2α activation and leads to increased PD-L1 translation (4). Similarly, Surech and colleagues have demonstrated that ISR stimulates PD-L1 mRNA translation in an eIF5B-dependent manner in non–small cell lung cancer (35). They showed that loss of uroporphyrinogen decarboxylase (UROD), a key enzyme in the heme biosynthesis pathway, induces ISR through a heme regulated inhibitor (HRI)–dependent manner (**Fig. 2**). Although eIF2α partially participates in the translational regulation of PD-L1 mRNA, eIF5B is required for the ISR-mediated PD-L1 mRNA translation upon heme deprivation. This adaptive translational upregulation of PD-L1 promotes lung cancer immune evasion with an approximately 50% reduction of CD8$^+$ T lymphocytes in the tumor microenvironment (TME).

Taken together, these studies have revealed novel regulation mechanisms of PD-L1 expression at the translational level in cancer cells and highlight a therapeutic opportunity offered by translational regulation mechanisms in the context of immunotherapies, which will be discussed further below (**Fig. 2**).

mRNA translation can modulate the antitumor immunity in immune cells

To combat against tumor cells, both innate and adaptive immune cells require fast responses to microenvironmental fluctuations and demand differential biomass synthesis depending on their metabolic status. Thus, it is expected that protein synthesis may be a critical regulatory mechanism in the immune cell compartment. In contrast to the studies on the PD-L1 translational regulation in tumor cells, the regulation of checkpoint inhibitor proteins (e.g., PD-1) in immune cells at the translational level has not been well characterized. However, recent studies have shown a critical role of mRNA translation in the process of T-cell maturation and the homeostasis of other types of immune cells. Bjur and colleagues first identified specific translation programs in CD4$^+$Foxp3$^+$ regulatory T cells (TFoxp3$^+$) and

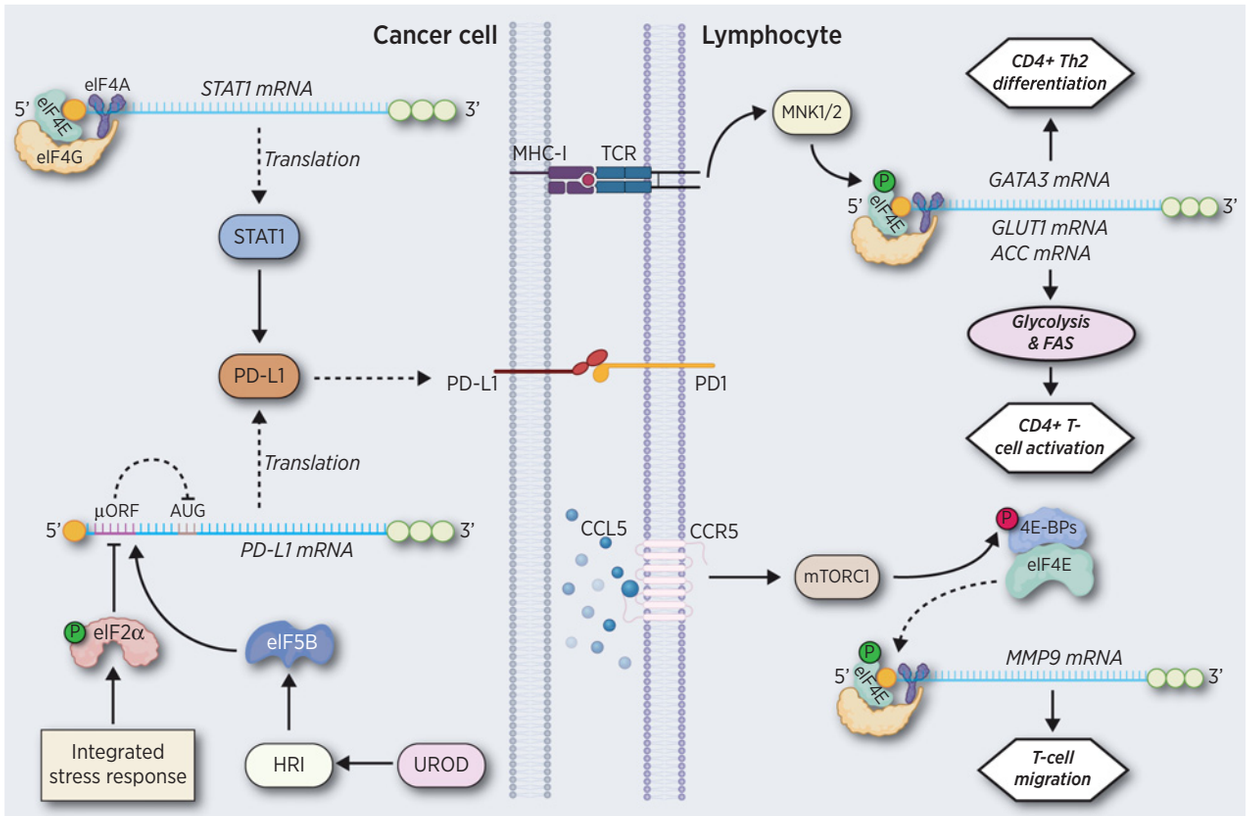

Figure 2.

mRNA translation participates in the regulation of antitumor immune response. In cancer cells, translation is implicated in regulating the immune checkpoint PD-L1 indirectly through a translational regulation of the transcription factor STAT1. Due to the presence of specific μORF in its 5′-UTL, the translation of PD-L1 mRNA can be upregulated by ISR in a eIF2α- or eIF5B-dependent manner. In lymphocytes, translation participates in $CD4^+$ Th2 differentiation and $CD4^+$ T-cell activation through the MNK1/2 dependent phosphorylation of eIF4E upon TCR engagement, which mediates the translation of specific mRNAs. Translation also participates in T-cell migration control by translational regulation of MMP9 via a CCR5/mTORC1/4E-BP1 axis. CCR5, C-C chemokine receptor type 5; GLUT1, glucose transporter 1.

$CD4^+Foxp3^-$ nonregulatory T cells ($TFoxp3^-$). Translational upregulation of eIF4E during T-cell activation activates the mRNA translation of cell proliferation–related proteins and Foxp3, emphasizing the underappreciated role of mRNA translation in $CD4^+$ T-cell fate decisions (36). Indeed, transcriptional state changes during T-cell activation require the cooperation of translational modulation. A recent large-scale genome-wide study combining 4-thiouridine sequencing, total RNA sequencing, and ribosome profiling during T-cell activation demonstrated that the majority of genes underwent coupled transcription and translation regulation (37). However, the translational activity during T-cell differentiation is not monotonic. Araki and colleagues showed that transcripts encoding translational machinery, including ribosomal proteins, were dynamically translated in $CD8^+$ effector T cells (Teff cells) during acute infection of mice with lymphocytic choriomeningitis virus. The mRNAs related to the cytotoxic function of T cells are translationally upregulated during T-cell clonal expansion and are probably required to sustain T-cell biomass requirements during rapid expansion. However, inhibition of translation was observed immediately before the contraction phase (10). Translation inhibition observed during terminal effector phase coincides with a step in which metabolism and proliferation are profoundly changed (38–40). An important remaining question is the causal relationship between the observed translational reprogramming and the T-cell homeostatic changes. Nevertheless, these studies highlight the dynamic regulation of mRNA translation during T-cell activation. Although the underlying signaling cues that trigger translational reprogramming in T cells are still not well defined, at least two studies have pointed to the possibility that T-cell receptor (TCR) engagement may induce the translation rewiring. Cook and Miller described a TCR-mediated translational upregulation of GATA binding protein 3 (GATA-3), a transcription factor controlling $CD4^+$ type 2 T-helper cell (Th2) differentiation (41). In another study, Gorentla and colleagues showed that MNK1/2, kinases, which phosphorylate eIF4E at serine 209 to promote cap-dependent translation, are activated by TCR-engagement (**Fig. 2**). This MNK1/2-mediated phosphorylation of eIF4E followed by activation of eIF4F translation initiation complex is required for $CD4^+$ T cell Th1 and Th7 differentiation (42). Apart from the direct phosphorylation of eIF4E by upstream kinases, eIF4F activity can also be modulated by its negative regulators 4E-BPs. The C-C motif chemokine ligand 5 (CCL5), a chemokine that participates in T-cell migration and chemotaxis, is able to control mRNA translation through a CCR5/mTORC1/4E-BPs pathway that leads to the translation initiation of cyclin D1 and matrix metallopeptidase 9 (MMP9) mRNAs (43). As suggested in this study, CCL5-mediated translation regulation probably enables rapid and efficient synthesis

of proteins from the existing pool of mRNAs required for T-cell migration (**Fig. 2**).

The maintenance of T-lymphocyte homeostasis requires a tight coordination between mRNA translation and energy production (intracellular metabolism). The mTOR-related pathway is well-known to be the master regulator of cell metabolism (44, 45), translation initiation and elongation (12, 46), and T-cell biology (47). However, the cross-talk between mRNA translation and T-cell metabolism goes beyond mTOR-regulated pathways. mRNA translation can be rapidly reprogrammed upon environmental fluctuations and can actively participate in the switch of T-cell metabolic status, which is demonstrated in the process of naïve T-cell activation upon TCR engagement. Ricciardi and colleagues identified a pool of untranslated mRNAs encoding metabolic enzymes for glycolysis and fatty acid synthesis (FAS) that accumulate in $CD4^+$ naïve T cells. The mRNA translational machinery is poised for a rapid activation, leading to the GLUT1 mRNA translation during T-cell activation (**Fig. 2**; ref. 48). Increased uptake of glucose resulting from the *de novo* GLUT1 translational upregulation promotes glycolysis. In the same study, the authors also found that the FAS activity is increased through further increasing acetyl-coA carboxylase 1 (ACC1) mRNA translation. This study suggests that mRNA translational repression plays an important role in keeping $CD4^+$ T cells in a quiescent naïve state and that the rapid response at the translational level upon TCR activation favors a complete metabolic switch toward a $CD4^+$ effector T-cell phenotype. Apart from translational regulation of glucose transporter expression, glycolytic enzymes, such as GAPDH, are also directly regulated at the translational level and implicated in effector T-cell function. Chang and colleagues have recently shown that GAPDH, which catalyzes the simultaneous phosphorylation and oxidation of glyceraldehyde-3-phosphate (G3P) to 1,3-biphosphoglycerate, can play a role as an RNA-binding protein and repress IFNγ translation by interacting with the adenylate-uridylate–rich region in the 3′ UTR of the IFNγ mRNA (49). Interestingly, because the catalytic site and the mRNA-interaction site of GAPDH are the same, the availability of the GAPDH substrate G3P can serve as a signal to modulate the interaction between GAPDH and IFNγ mRNA. GAPDH released from its classical enzymatic function can function in a nonclassical manner to engage the translation of IFNγ mRNA and thus participate in the regulation of effector T-cell functional. Thus, any signaling cues within the TME that impact the translation activities of T lymphocytes could reprogram their functional differentiation and, in turn, participate in tumor immune escape (**Fig. 2**).

Although most of studies on immune cell functions regulated at the translational level focus on the T lymphocyte, emerging roles of mRNA translation in other immune cell compartments are also attracting interest. By using IL15 to stimulate the antitumor function of natural killer (NK) cell in an adoptive transfer model, Mao and colleagues have shown that mRNA translation in NK cells is primed via IL15-mediated mTOR activation (50). Many of the mRNAs that are upregulated at the translational level in NK cells upon IL15 stimulation are implicated in electron transport chain and cellular respiration, thus underscoring the cross-talk between cytokine-dependent mRNA translation regulation and immune-cell metabolic control. This is important because chronic exposure to IL15 can induce NK cell hyporesponsiveness (51) and high concentrations of tumor cell–derived IL15 are associated with poor prognosis (52, 53). In the future, it will be important to study the possible role of mRNA translation in the response of NK cells to the prolonged stimulation with IL15 and in the immune escape by cancer cells. Innate immune cells, as the primary defense mechanism, require rapid responsiveness. Therefore, it is not surprising that, as observed in NK cells, mRNA translation is also found to be involved in dendritic cell (DC) activation (54). In fact, DC activation can be divided into two distinct phases from an mRNA translation point-of-view. While mRNA translation, and thus overall protein synthesis, is upregulated upon lipopolysaccharide (LPS)-induced PI3K signaling pathway activation during the early $CD11c^+$ DC maturation phase, it is inhibited in the following phase due to eIF2α phosphorylation. This dynamic translational regulation during distinct DC activation phases is important for DC resistance to apoptosis upon maturation and for peptide presentation through MHC-I.

These results suggest that mRNA translation is required for immune cell activation and primes a rapid and reversible immune response in the TME. Therefore, both tumor intrinsic and extrinsic regulation of mRNA translation may render cancer cells resistant to immunotherapy.

Translation Regulation Is Implicated in Resistance to Immunotherapies

Immunotherapy-based treatments, especially immune checkpoint inhibitors (ICI), have demonstrated their remarkable efficacy in several malignancies and have profoundly changed the practice of medical oncology. However, the majority of patients do not respond to these treatments (primary resistance) or relapse after an initial response (acquired resistance). Although antitumor immunity is a dynamic process that undergoes constant evolution in each patient, three main resistance mechanisms can be considered: (i) Impairment of antigen presentation; (ii) involvement of alternate immune checkpoints' (iii) recruitment of immunosuppressive cells to generate a permissive TME.

There is currently no consensus on biomarkers that can be used clinically to guide the selection of patients with cancer who potentially would respond to immunotherapy and to optimize the benefit/risk ratio of these therapies. However, high Tumor mutational burden (TMB) has been shown to have predictive value for identifying patients who likely would respond to immune checkpoint antibodies–based immunotherapy (55–58). Thus, pathways controlling genome stability and DNA repair appear to be crucial. Recently, a study has demonstrated that CDK12 cooperates with mTORC1 to phosphorylate the translation initiation complex inhibitor 4E-BP1 and thus stimulates translation of the DNA damage response (DDR) checkpoint kinase 1 (CHK1). The study has further identified a CDK12-dependent translational signature, which includes a set of mRNAs encoding factors essential for mitotic chromosome stability (59). Although additional studies will be necessary to fully understand the links among translation regulation, DDR and response to ICIs, this study suggests that translation could contribute to ICI sensitivity through controlling DDR.

ISR orchestrating stress adaptation has been implicated in cancer cell drug resistance (60). When ISR is activated, phosphorylated eIF2α attenuates global cap-dependent translation and concomitantly increases the translation of a subset of mRNAs that contain μORFs, such as the mRNA of the transcription factor ATF4. Interestingly, a study from Falletta and colleagues found that microenvironmental cues, particularly amino acid starvation, trigger transcription and translation reprogramming mediated by ATF4 and the translation initiation factor eIF2B, respectively, in melanoma cells, leading to downregulation of the microphthalmia-associated transcription factor (MITF) and upregulation of AXL receptor tyrosine kinase (61). This low MITF/high-AXL phenotype has been associated with the

resistance of melanoma cells to MAPK inhibitors (62, 63) and appears to also be able to arbitrate resistance to adoptive T-cell immunotherapy (61).

Among various mechanisms that mediate ICI resistance, reshaping the TME to obtain a cancer permissive stroma is one of the best characterized extrinsic resistance mechanisms (64). Recruitment or repolarization of immunosuppressive cells is the keystone of this mechanism. Among cells constituting the TME, macrophages, more specifically their polarization to M1-like or M2-like state, is a key determinant for the elimination or the development of the tumor (65). This differential polarization of macrophages has been extensively investigated to decrypt the physiologic and physiopathologic situations and several studies have shown a critical impact of mRNA translation in the macrophage-dependent inflammatory response (66). For example, the bromodomain-containing factor Brd4 has been shown to control an MNK2/eIF4E axis that stimulates the translation of IκBα mRNA, leading to decreased NF-κB–dependent inflammatory gene expression and thus compromising the innate immune response (67). In contrast, IFNγ modulates metabolism and mRNA translation during macrophage activation induced by toll-like receptors (TLR). Indeed, in TLR2-stimulated macrophages, IFNγ promotes inflammation via suppressing the translation of repressors of inflammation such as HES1 (68). Similarly, Cot/tpl2 (MAP3K8) has been implicated in the translational regulation of inflammatory mediators such as TNFα, IL6, and CXCL1 through the phosphorylation of 4E-BP1 (69).

The role of neutrophils in the premetastatic niche establishment is now well documented (70). mRNA translation also appears to be a key player in the regulation of neutrophil inflammatory function, the study of Lindemann and colleagues showed that, upon platelet-activating factor (PAF) activation, neutrophils can rapidly upregulate the translation of constitutive mRNAs, such as IL6 receptor alpha, without *de novo* transcription, to fulfill their functional homeostasis and to resolute injurious inflammation (71). In addition, the phosphorylation of eIF4E by MNK promotes neutrophil survival through stimulating the translation of the antiapoptotic proteins MCL1 and BCL2 and, thus, stimulates the formation of lung metastasis (72). Among different physiologic functions of neutrophils, the formation of neutrophil extracellular traps (NET), scaffolds of chromatin with proteases released into the extracellular space that trap microorganisms, have a determinant role in cancer metastasis (73–75) and can protect cancer cells from NK and $CD8^+$ T cell cytotoxicity. Thus, targeting NET formation could enhance the response of tumors to immunotherapy (76, 77). Interestingly, the mTOR pathway has been implicated in NET formation. Indeed, using pharmacologic inhibitors of mTOR, McInturff and colleagues have demonstrated that translational regulation of HIF1a is involved in NET formation (78).

Taken together, these studies have highlighted the key role that translation plays in intrinsic and extrinsic resistance of cancer cells to immunotherapies and offer the proof of concept that targeting mRNA translation might be an important potential approach to improve immunotherapy efficiency.

Therapeutic Challenges: Targeting mRNA Translation to Improve Immunotherapy Responses

Due to the essential role of mRNA translation in regulating both tumor intrinsic and extrinsic immune responses, modulating the mRNA translation with the aim of neutralizing cancer resistance to immunotherapy has great clinical importance. However, a series of barriers will need to be overcome in order to develop efficient and clinically useful mRNA translation-targeting strategies. In particular, targeting mRNA translation-associated pathways is frequently associated with undesired side effects. For example, rapamycin, an inhibitor of the mTORC1 pathway, inhibits the cap-dependent translation through downstream targets of mTORC1 S6 kinase and 4E-BPs and therefore can reduce the global mRNA translation. Because that S6 kinase and 4E-BPs play important regulatory roles in both cancer progression and immune-cell maturation, rapamycin can inhibit cancer progression but it also has an immunosuppressive activity (79). Thus rapamycin is a double-edged sword for the treatment of cancer (80).

The immunosuppressive effect of rapamycin may be a consequence of its effect on T-lymphocyte activity, which is particularly dependent on 4E-BP2, one of 4E-BPs, that is very sensitive to rapamycin via mTORC1 inhibition (81). Similarly, Chaoul and colleagues showed that rapamycin treatment can abolish vaccine-induced cytotoxic T-cell–mediated tumor elimination (82), which is possibly due to an indirect effect mediated by regulatory CD4 T cells (Treg). The immunosuppressive effect limits the efficacy of mTOR pathway inhibitors such as rapalogs in combination with vaccination approaches (83). On the other hand, rapamycin has been demonstrated to enhance the memory CD8 T-cell response (84). Consistently, combinations of immunotherapy with rapamycin (85, 86) or mTORC1 knockdown (87) have been demonstrated to eliminate tumors through a memory $CD8^+$ T-cell response. These results together suggest that inhibition of global mRNA translation may have distinct effects on immune cells depending on their differentiation status and imply that mRNA translation inhibition strategies for cancer therapy should consider both positive and negative effects on tumor cells and on microenvironmental cells. For example, to thwart the deleterious effect of mTOR inhibition, a triple combination of an mTOR inhibitor, vaccination, and CCR4 antagonist was proposed in order to limit Treg generation and to maximize antitumor immune response (83).

Another obstacle in treating cancers by inhibiting mRNA translation is the fact that stress-induced reprogramming of mRNA translation via the induction of the phosphorylation of eIF2α frequently leads to the alternative translation of ATF4. ATF4 has been shown to inhibit the melanoma master regulator MITF, whose down-regulation in melanoma cells is associated with increased invasiveness, dedifferentiation, drug resistance, as well as gene expression profiles associated with nonresponsiveness to anti–PD-1 immunotherapy (61).

Because of the complex upstream regulation of mRNA translation, strategies directly targeting mRNA translation machinery with high specificity appear to be more suitable to combat resistance to immunotherapy in cancers. Molecules that directly interfere with mRNA translation and have properties appropriate to be therapeutics (e.g., with restricted potential adverse events) are under development, though are still few. This approach has been under intensive investigation to target the eIF4F translation initiation complex. As phosphorylation of eIF4E is reported to lead to the translation of a mRNA subset that is implicated in cell transformation, proliferation, and invasiveness (21, 22, 88), targeting MNK1 and MNK2 responsible for eIF4E phosphorylation is one of the most developed strategies. Indeed, ribavirin, an FDA approved nucleoside analogue to treat hepatitis C, has been shown to sensitize renal cell carcinoma to IFNα immunotherapy by inhibiting eIF4E serine 209 phosphorylation (89). However, apart from its inhibitory effect of eIF4E phosphorylation, ribavirin has pleotropic effects, including inhibition of host inosine monophosphate dehydrogenase, lethal mutagenesis, and modulation of the host immune responses. More specific inhibitor of MNK1/2-eIF4E axis

may provide better benefit/risk ratio. An exquisitely selective MNK1/2 inhibitor eFT508 was recently developed (90). eFT508 treatment of mouse models of liver cancer strongly reduced PD-L1 mRNA translation and, as a consequence, induced increased cytotoxic $CD8^+$ T-cell infiltration in the tumors and reduce liver cancer progression (4). Moreover, because MNK1/2 are downstream effectors of the MAPK pathway, their inhibition could more specifically target the PD1/PD-L1 axis in MAPK pathway-dependent cancer cells than in immune cells, and thus avoiding many undesired consequence of using rapalogs. In line with this hypothesis, a recent study has elegantly shown that targeting MNK1 and MNK2 with eFT508 or SEL201, another MNK1/2 selective inhibitor, interferes with the melanoma phenotype switching responsible for tumor immune escape (3). This study demonstrated that inhibition of eIF4E phosphorylation reduced the mRNA translation of NGFR (3), a protein previously identified as a marker of the melanoma-initiating cells (91) that are resistant to immunotherapy (92). The study further showed that inhibition of the MNK1/2-eIF4E axis reprogrammed the TME by decreasing the production of inflammatory factors, which in turn lead to a decrease of PD-L1 expression in dendritic cells and MDSCs and a concomitant increase of $CD8^+$ T-cell tumor infiltration (3).

Another option to inhibit eIF4F complex is to target eIF4A, the RNA helicase responsible for unwinding the secondary structures in the 5′-UTR of mRNAs. This is exemplified by various natural compounds, such as flavaglines, hippuristanol, or pateamine A, that inhibit the eIF4A activity through diverse mechanisms (93–99). As described earlier, the eIF4F complex regulates PD-L1 expression via the translational regulation of STAT1. Pharmacologic inhibition of eIF4A by silvestrol, the primary member of the flavaglines family, potently suppressed STAT1-mediated PD-L1 expression in melanoma cells, thus blocking tumor-cell adaptative resistance to immune-cell attack through PD-L1 induction (6). However, silvestrol can be exported from tumor cells via the ABCB1/P-glycoprotein, rendering tumor cells resistant to silvestrol (100). To bypass this major drawback, derivatives with biological effects similar to those of silvestrol but lack the ability to interact with ABCB1 are being developed (101). Among eIF4A inhibitors, eFT226 has entered human clinical studies (102). eFT226 has been initially described to inhibit the translation of mRNAs encoding for oncogenic target genes (MYC, MCL1, BCL2; ref. 103). There is currently only a phase I/II trial evaluating the efficiency of eFT226 as monotherapy in solid tumors (NCT04092673). However, considering the role of eIF4F complex in the regulation of antitumor immunity (6), we can expect further clinical studies combining eFT226 and anti–PD-1 immunotherapy. This is the case for the pipeline of the MNK1/2 inhibitor eFT508, which is currently under investigation in combination with anti–PD-1 or anti–PD-L1 in patients who do not have an objective response to anti–PD-(L)1 therapy (NCT03616834). Thus, the results of these clinical trials will be critical in translating the targeting of mRNA translation for cancer treatment from the bench to the bedside.

Conclusions

As a central node of protein synthesis, mRNA translation is essential for cell homeostasis and adaptation. As such, mRNA translation contributes significantly to not only resistance mechanisms, intrinsic and extrinsic, of cancer cells but also effector T-cell activation and their antitumor functions. Thus, although the therapeutic window has to be carefully investigated because of pleiotropic cellular functions regulated at the translational level in various cell types, mRNA translation has emerged as an exciting therapeutic target to improve antitumor immunity and the efficacy of immunotherapy-based cancer treatment.

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